MEDIATION AND MODULATION OF FEBRILE AND ANTIPYRETIC HOST RESPONSES.

G.E. Resch, N.W. Kasting, W.D. Ruwe.

The neuronal mechanisms which modulate the 'acute phase response' generally and fever specifically continue to evoke increasing interest. In particular the investigation of functional inter-relationships between endogenous neuropeptides, transmitters and hormones suggest that more than one 'route of activation' functions through a complex neural network. Additionally, attenuative and permissive actions may be properties of the same molecules.

Dr. Kasting will discuss the role of vasopressin (AVP) as an endogenous moderator of febrile responses in ventral septal and other sites that are important to thermoregulation. Recent data show that indomethacin and salicylate, but not acetaminophen, administered iv increase plasma AVP levels. These observations do not exclude the classical mechanism of antipyretic drug action, inhibition of prostaglandin synthesis, but further suggest that AVP must be considered part of the mechanism of action of certain antipyretic drugs. Dr. Resch will review the antipyretic role of glucocorticoids and discuss recent data which show that cortisol serves a permissive role in modulating IL-1ß and PGE2, but not acetylcholine (ACh), induced elevation in body temperature. Similarly, α-MSH, shown to be antipyretic, may also have dual roles, eliciting heat gain from mPOA tissue sites and antipyresis by an icv route, acting in the septum and perhaps other sites. Dr. Ruwe will discuss macrophage inflammatory protein (MIP-1) which elicits fever, as do E. coli and IL-1ß, when injected into the ventral septal area (VSA), lateral cerebral ventricle, and the anterior hypothalamic area (AH/POA). Almost all sites show a concordance of sensitivity to PGE2 and the other pyrogens. Experiments with anisomyosin, a protein synthesis inhibitor, indicate the synthesis of new protein factors may be necessary for the induction of fever by E. coli, IL-1ß, or MIP-1. The data indicate differentiation between the mechanism of fevers elicited by different agents, ie. both ACh and PGE2 may mediate the initial phase of fevers induced by E. coli or IL-1ß but not MIP-1.

The cited data suggest a complex neural network composed of sites in the VSA and other areas, including the POA, near the lateral and third ventricles. These sites contain specific populations of unique neurochemically coded cells that may be responsible for different pathways leading to the development of the febrile response. The mediation and modulation of fevers of different etiologies could be integrated in this network. The data indicate different mechanisms, which imply different pathways, operate in the same neural network to elicit the common end point of fever or antipyresis.